REMARKS

Claims 1, 3, 5-11, 13-15, 36-49, 51, and 60-76 are pending. Claims 3, and 5-11 are withdrawn as they are directed to a non-elected species.

Examiner Interview

On September 17, 2009, Applicants' attorney, Janet S. Hendrickson, requested an interview to discuss the outstanding rejections. Since Examiner Levy refused the interview until after the due date for the response, Applicants request that the next action not be made final.

35 U.S.C. § 112

Reconsideration is requested of the rejection of claim 1, 13-15, 36-49, 51, 60-71, 73, 75, and 76 as not satisfying the enablement requirement of 35 U.S.C. § 112, first paragraph. Claim 1 is directed to a method of removing sodium from a human subject comprising administering to a human subject in need thereof an effective amount of a non-absorbed sodium-binding composition comprising a sodium-binding polymer. The sodium-binding polymer comprising at least one of polyvinylsulfonate polymer, polyvinylsulfamate polymer, polyvinylsulfamate/vinylsulfate copolymer, vinylphosphonate/acrylic acid copolymer, polyvinylsulfate polymer, or crosslinked polyvinylsulfamate polymer. The human subject is suffering from hypertension, chronic heart failure, end stage renal disease, liver cirrhosis, chronic renal insufficiency, fluid overload, or sodium overload.

The Office states that while the specification is "enabling for administering a crosslinked homopolymer of the instant claim 1, having the in vivo binding capacity of 4 mmol or more, to subjects with compromised kidney function, does not reasonably provide a basis for identification of an effective amount, for a given species, age, sex, of the now claimed polymers, in the open guise, to give, for any period of time, to any human or specific animal with any of the claimed diseases."[1]

Applicants submit that the specification contains support sufficient to enable those skilled in the art to practice the inventions of claims 1, 13-15, 36-49, 51, 60-71, 73, 75, and 76 without undue experimentation. The pharmaceutically active polymers of these claims are described in

[1] See Office action dated June 24, 2009 at page 2.

detail throughout the specification, particularly on pages 14-24, and methods of preparing these polymers are described, for example, on pages 24-25, and exemplified in Example 2 on pages 30-34. The specification also sets forth in detail the claimed methods of treatment on pages 25-27. All of these descriptions are written in clear and concise language using terms that are well-known to skilled persons.

Moreover, the specification describes on pages 6-14 and 25-27, that the polymers of the present claims remove sodium from the body by binding and removing the sodium from the gastrointestinal tract, that this sodium removal from the body affects the sodium concentration and water balance, and that the effect on sodium concentration and water balance has a beneficial effect for the claimed conditions. Although the Examiner states that the in vivo binding capacity of 4 mmol/g must be reinserted into claim 1, the requirement is repeatedly referred to as a preferred embodiment in paragraphs [0013] and [0016]. On pages 30 and 34-38, the specification details *in vitro* and *in vivo* tests to determine the activity of the pharmaceutical polymers. Further, the specification describes effective dosages and routes of administration on pages 27-30. These descriptions include the various modes by which the compounds can be administered to animals, the pharmaceutically acceptable forms in which they can be administered, and appropriate dosages for their administration. This information is sufficient to enable one skilled in the art to practice the inventions of the claims and accordingly, complies with the enablement requirement of 35 U.S.C. § 112.

A specification that contains a teaching of the manner and process of making and using the invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as an enabling disclosure unless there is reason to doubt the objective truth of the statements contained therein. As acknowledged in M.P.E.P. § 2164.04, the court in *In re Marzocchi* held that:

> "it is incumbent on the Patent Office whenever a rejection [for enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in the supporting disclosure and to back up such assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."[2]

In this case, the Examiner appears to be relying upon the breadth of the claims as a basis for doubting enablement. A rejection merely for breadth, however, is not appropriate, as explained

[2] *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

in *In Re Borkowski*,[3] *In re Robins*,[4] and in *Marzocchi* itself. Here, except for asserting that a person of skill in the art cannot identify an effective amount, the Office has not provided cogent reasoning to doubt applicants' specification. Thus, the Office has not met its burden of showing a *prima facie* case of lack of enablement under 35 U.S.C. § 112.

Applicants are not required to provide chemical or biological data as long as a description of each claimed invention is provided in clear and concise terms sufficient to enable a skilled person to practice each invention. Additionally, experimental examples are not required to support the complete scope of the claim. As stated in *In re Goffe*,[5] an applicant should not be required to limit the claims to materials disclosed in the examples because "[t]o demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts."[6]

Furthermore, and in any event, the experimentation required to test for the effective amount of a cation exchange polymer for each condition is not undue because a person of ordinary skill would know how to test for this using the guidance provided in the specification and such testing would be routine. Thus, claims 1, 13-15, 36-49, 51, 60-71, 73, 75, and 76 satisfy the enablement requirement of 35 U.S.C. § 112.

35 U.S.C. § 103 Rejection

Reconsideration is requested of the rejection of claims 1, 13-15, 36-44, 60-76 as unpatentable under 35 U.S.C. § 103(a) over EP 0349453 (Martani) in view of U.S. Patent No. 5,846,990 (Murugesan) and Notenbomer (EP 0730494). The Office asserts that Martani uses Eudragit polymers with added actives that would have removed sodium from a patient and that it would have been obvious that Martani discloses oral formulations but not the disease states. The disease states are said to be disclosed by Murgesan with associated drugs and polymers similar to

[3] 164 U.S.P.Q. 642 (C.C.P.A. 1970).
[4] 166 U.S.P.Q. 552 (C.C.P.A. 1970).
[5] 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976).
[6] See id. at 431.

Martani's polymers are said to be disclosed by Notenbomer, and supposedly the Notenbomer compositions are known to lower sodium levels.[7]

Initially, the determination of whether a claim is obvious under 35 U.S.C. § 103 depends on at least four underlying factual issues set forth in *Graham v. John Deere Co. of Kansas City*[8]: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) evaluation of any relevant secondary considerations. In April 2007, the Supreme Court affirmed the *Graham* analysis as the framework for determining obviousness.[9]

In addressing the scope and content of the prior art, references are not pertinent to an obviousness inquiry if they are not from analogous art.[10] A reference is analogous art if: (1) the reference is from the same field of endeavor, regardless of the problem addressed, or (2) the reference is not within the inventor's field of endeavor, yet it is reasonably pertinent to the particular problem addressed by the inventor. In *Clay*, the PTO asserted that the claimed invention and the Sydansk reference were part of a common endeavor of "maximizing withdrawal of petroleum stored in petroleum reservoirs."[11] Sydansk taught the

> use of a gel in unconfined and irregular volumes within generally underground natural oil-bearing formation to channel flow in a desired direction; Clay teaches the introduction of gel to the confined dead volume of a man-made storage tank.[12]

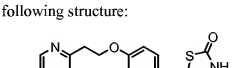
However, the Federal Circuit disagreed with the Office and held that Clay's field of endeavor was "*storage* of refined liquid hydrocarbons" and Sydansk's invention was directed to the "*extraction* of crude petroleum."

The second step of the *Graham* analysis requires consideration of the differences between the prior art and the claims at issue. It is well established law, that, where, as here, the patent at issue claims a chemical compound, the analysis of the *Graham* factor i.e., the differences between the claimed invention and the prior art, often turns on the structural similarities and differences between the claimed compound and the prior art compounds.[13] Obviousness based

[7] See Office action dated June 24, 2009 at page 3.
[8] 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966).
[9] *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007).
[10] *In re Clay*, 23 U.S.P.Q.2d 1058, 1060 (Fed. Cir. 1992).
[11] *Id.*
[12] *Id.*
[13] *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377; 81 USPQ2d 1324 (Fed. Cir. 2006).

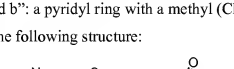
on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.[14]

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*,[15] the Federal Circuit addressed the obviousness issue for structurally similar chemical compounds. In *Takeda*, the claim at issue recited pioglitazone (5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione) having the following structure:



The ethyl substituent is attached to the 5-position on the pyridyl ring.

Alphapharm filed an ANDA to manufacture and sell a generic version of pioglitazone. According to Alphapharm, Takeda's claimed compound would have been obvious over the prior art compound TZD ("compound b": a pyridyl ring with a methyl (CH_3) group attached to the 6-position of the ring),[16] having the following structure:



Alphapharm argued that one of ordinary skill in the art would select compound b for antidiabetic research and then make "two obvious chemical changes: first, homologation, i.e., replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, 'ring-walking,' or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone."[17]

The district court found, however, that one of ordinary skill in the art would not have selected compound b from the "hundreds of millions" of possible compounds. "[T]he prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as

[14] *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356; 83 USPQ2d 1169 (Fed. Cir. 2007).
[15] 492 F.3d 1350 (Fed. Cir. 2007).
[16] *Id.* at 1354.
[17] *Id.* at 1357.

the lead compound for antidiabetic research."[18] The Federal Circuit affirmed and held that there was no motivation to select a particular prior art compound (e.g., compound b) from the universe of prior art compounds and even if there was such a motivation, nothing in the prior art would have led a skilled person to modify compound b to arrive at the claimed compound. Thus, when determining the obviousness of new chemical compounds, there must be "some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness."[19]

Once a reason to modify a known compound is found, the skilled person must also have a reasonable expectation that such a modification will be successful or beneficial in some way. In many chemical cases a "reasonable expectation of success" is not always found, as the Federal Circuit stated in *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*[20] :

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable. (Emphasis added)

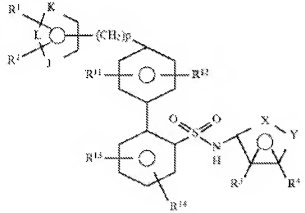
Martani discloses compositions for the prolonged *release* of various cationic or anionic active ingredients. The cationic active ingredients are loaded on various anionic resins, particularly, polystyrene sulfonate resin and then the polystyrene sulfonate-active ingredient

[18] *Id*, at 1358.
[19] *Id.*
[20] *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008).

complex is coated with either an anionic (e.g., Eudragit® S) or preferably, a cationic (e.g., Eudragit® RL) polymer coating to delay the release of the active ingredient once administered. For anionic active ingredients, a cationic resin such as cholestyramine is used to complex the active ingredient and an anionic polymer coating (e.g., Eudragit® S) is used to coat the cholestyramine-active ingredient complex. Martani discloses acrylate/methacrylate copolymers (e.g., Eudragit), polystyrene sulfonate and poly(acrylic acid) (e.g., Carbomer) as cation exchange polymers.

The specific cation exchange polymers specified by claim 1 would not have been obvious from the Martani disclosure. Martani is concerned with controlled release of various active ingredients that are ionic. For this purpose, polystyrene sulfonate is exemplified, but Martani provides no disclosure that would have led a person of ordinary skill to select the particular cation exchange polymers required by claim 1 from the universe of possible cation exchange polymers. Further, Martani does not disclose or provide a reason to use the composition for treatment of a subject having any of the claimed conditions (e.g., hypertension, chronic heart failure, end stage renal disease, liver cirrhosis, chronic renal insufficiency, fluid overload, or sodium overload) and in need of such treatment. Thus, the Martani disclosure would not have provided a skilled person with a reasonable expectation that the claimed compositions would be useful to treat a subject having any of the claimed conditions.

Murugesan discloses various small molecule sulfonamide compounds having the following formula:



These sulfonamides are described as endothelin antagonists useful to treat hypertension. While the Murugesan compounds are said to be useful to treat hypertension, a person of skill in the art

would not have had a reason to combine the disclosure of Murugesan with Martani because the small molecules of the Murugesan sulfonamides are absorbed and act as endothelin antagonists. Such small molecule receptor antagonists' mechanism of action is to block the endothelin receptor sites to inhibit the effects of endothelin, an effective vasoconstrictor. In contrast, the sodium-binding polymers of the claimed invention are not absorbed from the gastrointestinal tract and they bind and remove sodium from the animal's system. One of ordinary skill would have had no more reason to combine Murugesan with Martani than to combine any other reference describing a compound useful for treating hypertension with Martani. Absent some reason to combine the disclosures of the cited references, no *prima facie* case of obviousness has been established.

Notenbomer generally discloses methods and particles for binding monovalent cations. The particles have a nucleus and a coating; the nucleus contains a cation exchange material and the coating comprises a membrane that is permeable for monovalent cations. This coating is disclosed as being more permeable for monovalent cations than for bi- or higher valent cations. Disclosed cation exchange polymers are polycarboxylates, polymaleinates, polyacrylates, polyacrylate-co-maleinates, polyphosphates, polysaccharides, cellulose, starch, pectins, alginate, and sulphonated polyvinylstyrenes. Exemplified cation exchange materials are polyphosphate and polystyrene sulfonate resins and exemplified coatings are cellulose acetate and polyethyleneimine. These particles can be used to treat hypertension.

Notenbomer does not remedy the deficiencies of the Martani and Murugesan references. The disclosed and exemplified cation exchange polymers do not disclose or teach the cation exchange polymers of claim 1. Further, such disclosure would not have led a person of ordinary skill to select the polymers of claim 1 from the universe of cation exchange polymers. Thus, the Notenbomer disclosure would not have provided any reason alone or in combination with Martani and/or Murugesan why the polymers of claim 1 would be beneficial to treat the claimed disease states.

Finally, the office asserts that there are "no unobvious and/or unexpected results obtained" because the prior art discloses use of cation exchange polymers.[21] However, as detailed above, the Office has failed to establish a *prima facie* case of obviousness because it has

[21] Office action dated June 24, 2009 at page 4.

provided no reason why a skilled person would have combined the cited references to arrive at the claimed methods. Since no *prima facie* case of obviousness has been established, applicant need not show unexpected results. Thus, claims 1, 13-15, 36-44, 60-76 as patentable over EP 0349453 (Martani) in view of U.S. Patent No. 5,846,990 (Murugesan) and EP 0730494 (Notenbomer) under 35 U.S.C. § 103(a).

Rejoinder

Pursuant to MPEP §821.04, Applicants again request rejoinder of withdrawn claims 3, 5-11 as they depend from claim 1, require all of the limitations of claim 1, and claim 1 is amended to include specific acid resin polymers. Furthermore, applicants submit that these claims are allowable over the references relied upon by the Office.

CONCLUSION

Applicant submits that the present application is in condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,

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